A Lifecourse Approach to Prevention of Obesity and Type 2 Diabetes in Adolescence

HYPOTHESES SUBMITTED TO NCS STUDY DESIGN WORKING GROUP AND FEDERAL ADVISORY COMMITTEE

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Contact

Matthew W. Gillman, MD, SM (Non-federal Chair of Early Origins of Adult Health WG)
Associate Professor
Department of Ambulatory Care and Prevention
Harvard Medical School/Harvard Pilgrim Health Care
133 Brookline Ave., 6th floor
Boston, MA 02215
Phone 617 509-9968 (assistant Rachel Fournier)
617 509-9900 (main department number)
Fax 617 509-9853
E-mail matthew_gillman@hms.harvard.edu

Other members of EOAH Working Group contributing to this document:

Nancy Potischman, NCI (Federal Chair)
Peter Bennett, NIDDK
Ellen Demerath, Wright State U.
Boyd Metzger, Northwestern U.
Nicolas Stettler, Children's Hosp. of Phila.
Ken Schoendorf, CDC/NCHS, ICC Liaison

Members of other Working Groups contributing to this document:

Christine Bachrach, NICHD, Co-Chair, Social Environment Working Group
Molly Bray, U. Texas Houston, Gene-Environment Working Group

I. Introduction/General Principles

The Early Origins of Adult Health Working Group has developed a list of principles that should govern hypothesis formation regarding research on early origins of adolescent and adult health. The overarching principles are that susceptibility to adult chronic disease is determined by a dynamic process that occurs over the lifespan. Perturbations ("insults") that determine adult health states may occur anywhere from pre-conception to embryonic, fetal, infant, childhood, adolescent (and adult) life. These insults can affect both somatic growth and maturation of metabolic systems, and they include a range of determinants, including societal, lifestyle, and biological. These determinants act in concert with each other.

The "lifecourse approach to chronic disease" is what some have dubbed the scientific approach that arises from these principles. We find this term useful, as it reminds us to formulate our hypotheses from these principles and to recommend overall study design features to the NCS.

This approach allows determinants to work in several different ways. One classification scheme groups conceptual models under 4 headings[1]:

- A critical period model, in which an insult during a specific period of development has lasting effects on the structure or function of organs, tissues and body systems. Some prefer to call these periods sensitive rather than critical if the insult is not completely deterministic.
- A critical period model with later effect modifiers
- An accumulation of risk model where insults are independent and uncorrelated
- An accumulation of risk model where insults are correlated either through clustering or as part of a biological and/or social pathway ("chains of risk").

Implications for overall study design of this and other general principles espoused by the EOAH WG are found in our WG charge and in hypotheses we submitted to the study design working group on 4/1/02, both available on the portal. In this document, we apply the principles to a set of specific hypotheses on development of adolescent obesity and type 2 diabetes. We believe that these interrelated hypotheses help to form a sound justification for conduct of the National Children's Study.

II. Specific Hypotheses Related to a Lifecourse Approach to Prevention of Obesity and Type 2 Diabetes in Adolescence

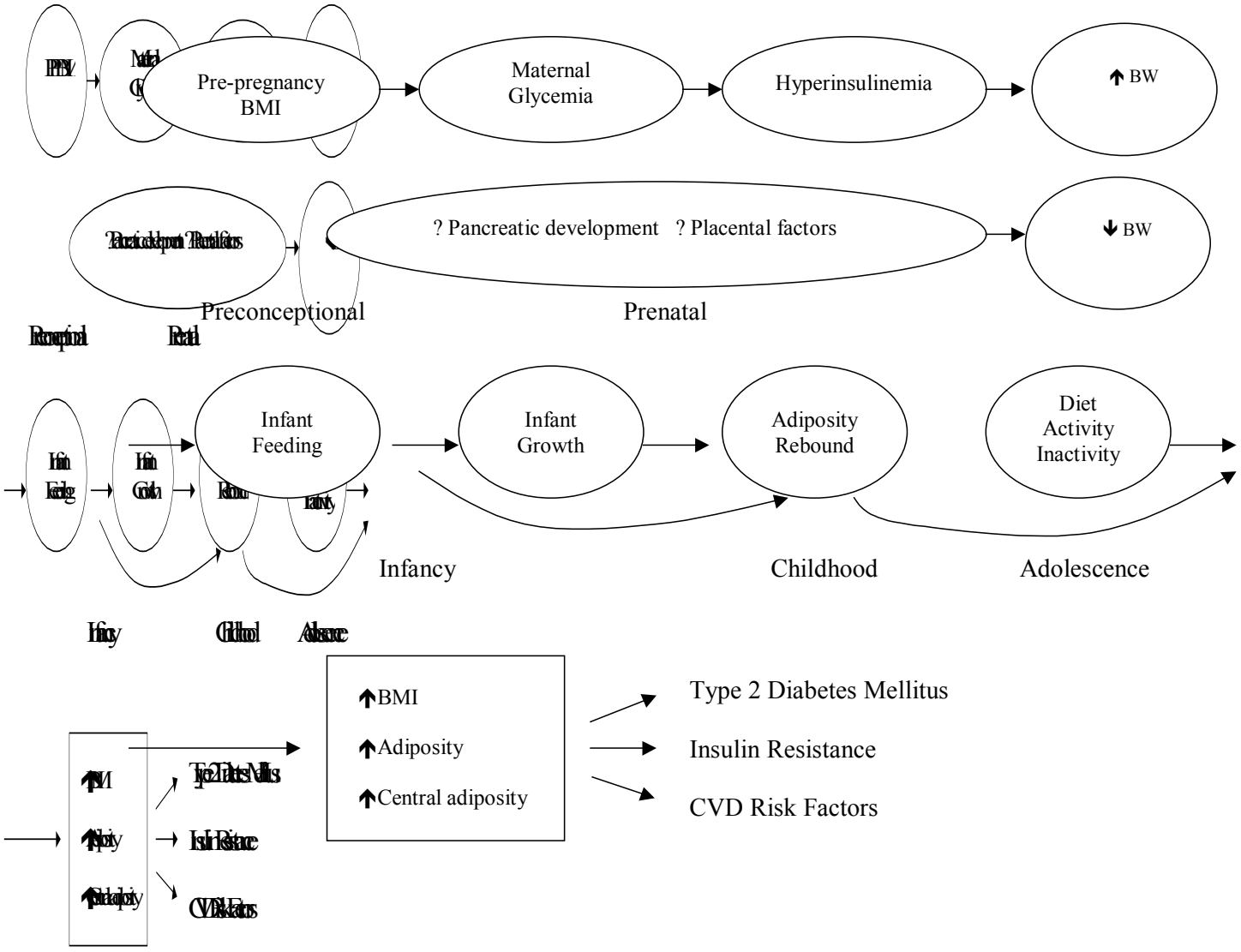
Proposed Core Hypotheses / Questions

In the past 4 decades, the prevalence of obesity in US children and adolescents has risen dramatically.[2,3] Childhood obesity is not benign. Most importantly, it is the single strongest predictor of type 2 diabetes, which also appears to be rising at an alarming rate among adolescents. In addition, childhood and adolescent obesity predict adult obesity and its serious sequelae as well as short-term morbidities such as hypertension, dyslipidemia, the insulin resistance syndrome, sleep apnea, early puberty, possibly asthma, and adverse psychosocial consequences.[4-6] The current epidemic of childhood obesity and incipient epidemic of adolescent type 2 diabetes call for interdisciplinary studies of its early life origins. Only with such studies will we be able to design effective preventive strategies.

The lifecourse approach to chronic disease fits very well with studies of the origins of obesity and adolescent type 2 diabetes. Figure 1 shows a schematic of potentially etiologic exposures that could occur from the preconceptional period through adolescence. Many of these exposures could interact with each other to cause disruption of energy balance and, therefore, excess weight gain through childhood. Further, for development of obesity and type 2 diabetes, critical or sensitive periods may exist during fetal life and childhood.[7] During these periods, insults could cause more long-lasting risk for obesity than they would at other times, either because target tissues are going through critical developmental stages, they are growing rapidly, or other reasons. Examples of these periods may include fetal life, during which organ systems undergo much of their maturation; infancy, during which feeding practices may determine long-lasting habits or metabolism; mid-childhood, when adiposity rebound ("loss of baby fat") occurs; and around the time of puberty, which incorporates a major growth spurt and alterations in endocrine axes.

The hypotheses we enumerate below are selected from a large number that require the resources, size, and follow-up period of the proposed NCS. They reflect the concepts embodied in the lifecourse approach, including a wide range of determinants, interactions among determinants, dynamism over time, and the possibility of critical or sensitive periods.

Figure. Lifecourse Approach to Development of Adolescent Obesity and Type 2 Diabetes



Proposed specific hypotheses:

1. Prenatal period:

1.1 Exposure to increased maternal glycemia, known to cause accelerated fetal growth, programs the fetus for development of obesity and adolescent type 2 diabetes. The relationship of maternal glycemia to offspring obesity/diabetes is graded. Thus this association is not limited to frank gestational diabetes, but also occurs at lower levels of glycemia. This association persists after controlling for inherited genetic factors related to both maternal and offspring hyperglycemia.

1.2 On the other end of the birth weight spectrum, embryonic and/or fetal growth restriction is associated with development of central obesity, measures of insulin resistance, and the insulin resistance syndrome in the child, after adjusting for attained body mass in adolescence. These associations are mediated by placental dysfunction.

1.3 The relative proportion of adipose and lean tissue, independent of overall body size at birth, predicts adolescent obesity and type 2 diabetes.

2. Infancy:

2.1 Breast milk feeding, compared with infant formula feeding, and breastfeeding duration are associated with lower rates of obesity and lower risk of adolescent type 2 diabetes. This association persists after controlling for sociocultural determinants of both breastfeeding and obesity. This association is mediated by both behavioral and hormonal mechanisms.

2.2 After controlling for gain in length, rapid weight gain during infancy in full-term infants is associated with childhood and adolescent obesity and type 2 diabetes. By contrast, gain in length during infancy is not associated with later obesity. The association of rapid weight gain with later obesity is primarily explained not by genetically determined catch up growth, but by postnatal environmental factors, chiefly type and duration of infant feeding.

3. Early childhood:

3.1 Earlier age at true adiposity rebound, not just BMI rebound, is associated with the development obesity and type 2 diabetes in adolescence. Some, but not all, of this phenomenon is explained by upward crossing of adiposity percentiles at earlier ages. Age at adiposity rebound is a predictor of later obesity independent of either adiposity level at that age or adiposity level at a specified age, eg, 7 years.

3.2 Predictors of earlier age at adiposity rebound include 1) rapid increase in relative weight or adiposity during infancy, and 2) reduced breastfeeding rate or duration.

4. Later childhood and adolescence:

4.1 Dietary predictors of gain in adiposity include reduced intakes of fiber and whole grains, and high glycemic index. Quality of carbohydrate is more important than quantity in determining incidence of obesity and type 2 diabetes.

4.2 In terms of inactivity, television and video watching are stronger predictors of weight gain than is personal computer use. Inactivity and physical activity are independent predictors of weight gain.

4.3 Determinants of physical activity include personal, social, and environmental factors. Teenagers who participate in individual activities requiring limited resources, such as running and biking, experience a less steep decline in activity levels during adolescence than teenagers who participate in team sports or activities requiring more resources, such as swimming.

Environmental factors such as distance to parks, availability of walking routes in the neighborhood, and neighborhood safety are associated with physical activity levels and, thus, development of obesity and type 2 diabetes.

4.4 Physiologic sequelae of obesity in adolescence are serious. Obesity is associated with increased left ventricular mass, independent of blood pressure level. Greater fat mass, especially in the central region, but not lean mass, is associated with insulin resistance, the insulin resistance syndrome, endothelial dysfunction, and type 2 diabetes.

Public Health Significance:

Obesity and its complications, particularly type 2 diabetes, are rapidly increasing in the US, reaching epidemic proportions in children, adolescents, and young adults, especially in minority populations.[2,3] As obesity and type 2 diabetes are associated with some of the most frequent causes of morbidity and mortality in the US, and as the treatment of obesity is often unsuccessful, the prevention of obesity is a public health priority (Healthy People 2010). A clear understanding of the determinants of obesity is needed to develop effective preventive strategies. The modern epidemic of obesity and type 2 diabetes in childhood and adolescence started to emerge after the end of the National Collaborative Perinatal Project, the last large US national prospective birth cohort study. Therefore, the hypotheses related to these new pediatric public health problems should be addressed in a contemporary US birth cohort. The NCS will offer a unique opportunity to identify early life determinants of obesity and its sequelae, including adolescent type 2 diabetes.

The public health significance of obesity and diabetes was recently emphasized by HHS Secretary Tommy Thompson, when he announced a new initiative to promote healthy communities in early 2002. "Too many Americans suffer the daily effects of diabetes, [asthma] and obesity. Perhaps the greatest tragedy is the increasing toll … these afflictions are taking on our children," Secretary Thompson said. "Focusing on prevention is one of our major goals at HHS. The number of persons with diabetes in the United States has nearly doubled in the past decade to affect 16 million people. The number of cases of obesity in the United States has increased more than 50 percent over the past two decades. Diabetes is the seventh leading cause of death in the United States and is also associated with heart attack, stroke, blindness and loss of limb. Obesity is associated with an increased risk of heart disease, cancer, arthritis, diabetes and asthma."

Further background about the epidemic of obesity and its complications in the US is available in the obesity hypothesis submitted by the Gene-Environment Working Group (Molly Bray, contact).

Justification for a Large, Prospective, Longitudinal Study

1. **Large.** It is helpful to have precise prevalence estimates of exposures and outcomes to justify a large sample size. As of yet, however, there are no adequately sized population-based studies in the US to estimate the current prevalence of adolescent type 2 diabetes. The best estimate from NHANES III, covering the years 1988-1994, suggests a prevalence of approximately 0.25-0.5% among approximately 3000 12-19 year olds.[8] In the Pima Indians, in which type 2 diabetes is endemic, approximately 2% of 10-14 year olds and 5% of 15-19 year olds had diabetes, mostly type 2, in the mid-1990's.[9] Clinic-based studies suggest a possible 10-fold increase in its prevalence of the past 20 years.[9] For our power calculations, below, we assume that the 0.5% from NHANES III is probably a minimum estimate, and that 5.0% from the Pimas is a maximum. We also calculate power for a prevalence of 1.0%, perhaps more realistic for the general population. Estimates for obesity (BMI >95th percentile for age and sex) in the 10-20% range in adolescence are more readily available from population-based data.[2,3]

   In addition, previous studies of adolescent and adult obesity and diabetes tell us that sample sizes of 10,000-25,000 are inadequate to address the main effects for obesity as an outcome, much less type 2 diabetes, which is less common, or possible effect modification by, say, sex, race/ethnicity, and genetic markers. For example, in a study of more than 10,000 Israeli men, the odds ratio (OR) for adolescent overweight in those born with high vs. normal or low birth weight was 1.30 (95% CI 1.07–1.59).[10] However in the offspring of diabetic mothers, the 95%CI of the OR was much larger—0.62–10.1—not allowing meaningful conclusions about maternal glycemic status as a possible effect modifier. In a recent study of over 15,000 US boys and girls, the OR for adolescent obesity was 1.3 (95% CI 1.1-1.5) for each 1 kg increment in birth weight, after adjustment for confounding factors, including maternal BMI.[11] The OR for adolescent obesity for maternal gestational diabetes (v. no maternal diabetes) was 1.2, but with a wide 95% CI (0.8-1.7) While a 20% increase in obesity risk may be large from a public health standpoint, even a study of this magnitude could not distinguish that estimate very well from larger or smaller, even null, effects. In another relatively large study, of 22,846 60-year old US men, compared with the subjects with an average birth weight, the OR for type 2 diabetes for those with a relatively low birth weight was 1.70 (95%CI 1.17–2.48), and for those with a relatively high birth weight OR = 0.71 (95% CI 0.32–1.05), after controlling for achieved body mass in adulthood.[12] These relatively wide confidence intervals, despite a substantial sample size, preclude definitive conclusions.

   For our power calculations, we choose one of our hypotheses, namely, that maternal gestational diabetes predicts adolescent obesity and type 2 diabetes in the offspring. Prevalence of gestational diabetes was 3-4% in some US populations in the 1980's-1990's,[11] but could be higher, say 6%, during the tenure of the NCS.

   We thus make the following assumptions:

   Prevalence of maternal gestational diabetes: 3, 6%
   Prevalence of adolescent obesity: 10, 15, 20%
   Prevalence of adolescent type 2 diabetes: 0.5, 1, 5%
   Odds ratios of interest: 1.2, 1.5, 1.75, 2.0
   Alpha level: 0.05

Sample sizes: 100,000 = total study sample; 12,500 = subjects in each of 2 sex and 4 equally sized race/ethnicity strata (For simplicity, we also assume equal prevalence in all race/ethnic groups, but in reality black and Hispanic adolescents will probably have higher prevalence of both obesity and diabetes.[2]

The table below shows power estimates for the various combinations of these assumptions, for each of the 2 outcomes separately.

Table. Power to detect associations of maternal gestational diabetes with offspring obesity or adolescent type 2 diabetes. The first estimate in each cell is for maternal gestational diabetes prevalence of 3%, the second for 6%.

Obesity
n=12,500

	Obesity Prevalence		
OR	10%	15%	20%
1.2	.21/.35	.27/.45	.31/.53
1.5	.74/.94	.85/.98	.91/1
1.75	.95/.99	.98/1	.95/1
2.0	.99/1	.95/1	.99/1

Type 2 Diabetes
n=12,500

	DM Prevalence		
OR	0.5%	1.0%	5.0%
1.2	.06/.07	.07/.09	.14/.22
1.5	.14/.19	.20/.29	.52/.76
1.75	.23/.32	.33/.49	.79/.96
2.0	.32/.45	.46/.67	.93/.99

Obesity
n=100,000

	Obesity Prevalence		
OR	10%	15%	20%
1.2	.87/.99	.95/1	.98/1
1.5	1/1	1/1	1/1
1.75	1/1	1/1	1/1
2.0	1/1	1/1	1/1

Type 2 Diabetes
n=100,000

	DM Prevalence		
OR	0.5%	1.0%	5.0%
1.2	.13/20	.21/.33	.63/.88
1.5	.47/.71	.72/.92	1/1
1.75	.74/.93	.94/.99	1/1
2.0	.90/.99	.99/.99	1/1

What this table shows is that for the outcome of obesity, power to detect an odds ratio of 1.5 or higher is adequate within sex and race/ethnicity-specific strata of 12,500 each. However, for a smaller odds ratio of 1.2, which is probably still important from a public health perspective, power is marginal even with the larger estimates of 6% for gestational diabetes and 20% for obesity.

For the outcome of type 2 diabetes, for the sex and race/ethnicity-specific strata, power is adequate only if both the outcome prevalence and odds ratio are both on the high end. For the whole study population of 100,000, power to detect odds ratios of 1.5 and above are quite adequate. But for an odds ratio of 1.2, probably important for public health, power is inadequate unless the exposure and outcome prevalences are quite high.

Implications of these power analyses for our proposed hypotheses are as follows:

1. For exposures at least as prevalent as maternal gestational diabetes, and outcomes at least as prevalent as adolescent type 2 diabetes, the projected 100,000 sample size is adequate for odds ratios of interest for main effects.

2. Within sex and race/ethnicity-specific strata, power becomes marginal for main effects when exposures are as uncommon as maternal gestational diabetes, even for relatively common outcomes such as obesity, if we are interested in odds ratios much below 1.5. Fortunately, many of the exposures we hypothesize are more common than this one.

3. Within sex and race/ethnicity-specific strata, power for further investigation of effect modification (interaction) will be limited.

4. In addition to the large sample size needed for main effects and effect modification by time-independent covariates such as sex and race/ethnicity, the time-varying nature of the lifecourse approach also necessitates a large sample size. For example, we hypothesize that not only excessive weight at one point in time is an important determinant of obesity/type 2 diabetes, but that the trajectory that leads to this excessive weight may also be critical. Therefore, the interaction of the successive growth patterns during fetal life, infancy, and later childhood may give us more information than any one period alone. For example, the impact of rapid infancy weight gain may be different in subjects born after fetal growth restriction than those who were not. In addition it is important to assess how genes, diet, and physical activity mediate or modify the association of early life growth with the development of obesity and adolescent type 2 diabetes.

Overall, then, a NCS sample size of 100,000 is clearly justified for examination of the hypotheses we propose. It is certainly not too large, and for examination of some interactions of interest, may indeed be too small.

2. **Prospective.** Prospectively collected data are needed for reliable information on many exposures of interest, eg, maternal diet during pregnancy, placental specimens, and infant and childhood anthropometry and blood specimens. Historical cohorts lack many variables of current scientific interest. Prospective data collection decreases the risk of recall bias, which could be substantial with the kinds of exposures that we propose, e.g., duration of breastfeeding.

3. **Longitudinal.** Development of obesity and type 2 diabetes is inherently a longitudinal issue. Data are required from many timepoints along the lifecourse, and informed approaches to longitudinal data analysis are necessary.

Scientific Merit

Previous studies in this area have been limited by inadequate sample size, incomplete assessment of covariates, samples unrepresentative of the diverse US population, relatively short follow-up intervals, or a combination of these factors. In fact, to date, there is no single study that combines data from the prenatal period with early feeding and childhood growth information and follows children into adolescence.

The NCS will offer a unique and powerful opportunity to investigate the development of adolescent obesity and type 2 diabetes in a large, diverse, US population. Identification and quantification of determinants of these two important public health problems will lead to new paradigms for prevention. Especially important are the principles espoused by the lifecourse approach: determinants occur throughout developmental stages; they may span domains from environmental to societal, lifestyle, and biological, including genetic; and they interact with each other.

Further, it will not be necessary to wait the entire 20 years of planned followup to analyze data of importance to the development of obesity and type 2 diabetes. For example, while obesity during adolescence is more predictive, obesity earlier in childhood is still a strong predictor of adult obesity. Cardiovascular risk factors associated with obesity, such as blood pressure and lipids, are well known to track from mid-childhood to adulthood. Lifestyle factors such as dietary and physical activity habits, also track through childhood. For these reasons, examining intermediate outcomes even in early to middle childhood will contribute to the evidence base leading to reducing the health burden of obesity and its complications.

New prevention strategies will take advantage of emerging data from this study. For example, population based strategies may attempt to alter biological processes by modifying the environment rather than attempting individual behavior change through education. In the clinical arena, risk stratification based on effect modification by, say, genetic factors, could lead to tailored pharmaceutical strategies to prevent the sequelae of obesity and diabetes. In addition, these investigations could not only test hypotheses from animal and other biomedical studies, but generate mechanistic etiologic hypotheses as well.

Potential for Innovative Research

A lifecourse approach to the understanding of chronic disease is an important addition to the classical epidemiologic approach of identifying lifestyle risk factors. It involves notions of critical periods, in particular regarding long-term effects of altered fetal environment, but also intersecting domains of determinants in a dynamic fashion throughout developmental stages both before and after birth. This paradigm shift is likely to lead to novel strategies for the prevention of conditions as frequent as obesity and type 2 diabetes, both population and high-risk strategies, aimed at women of reproductive age as well as their children.

The mechanisms underlying the association between early life factors and chronic disease, such as obesity, type 2 diabetes, hypertension, and cardiovascular disease remain largely unknown, and are currently investigated mainly in animal models and in smaller clinical and epidemiologic studies. Extension of these new hypotheses and rapidly evolving technology to the NCS will lead to innovative epidemiological research strategies.

The following methods will also need to be developed, standardized, validated, or refined for use in the NCS: repeated fetal ultrasound to measure infant growth and the growth of specific

organs; approaches to placental pathophysiology; assessment of diet and activity in mothers and children; assessment of body composition and of fat distribution in infants and young children; assessment of early markers for cardiovascular complications of obesity, such as endothelial function; improvements in genomics and proteomics; investigation of gene-environment interactions; improvements in assessment of social-environmental determinants through geocoding and other methodologies; and development of appropriate statistical methods for the lifecourse approach to adolescent and adult health.

Potential for Synergy with Other Working Groups

The EOAH Working Group has collaborated with the following other WGs in the genesis of these hypotheses: Gene-Environment Interaction; Social Environment; and Nutrition, Growth, and Development. Both the GEI and SE Working Groups will have submitted hypotheses that complement the ones in this proposal. Others may be interested as well, including Mid and Late Pregnancy (Pregnancy and the Infant); Asthma; Infection and Immunity.

Feasibility

Repeated measurements of pre- and post-natal growth and body composition will be required to answer the proposed hypotheses. Prenatal growth is assessed by repeated fetal ultrasounds. Although large-scale, standardized measurements of fetal growth have not been conducted in the US, there is a large clinical experience with this technique. Not only are ultrasounds non-invasive, but they can have benefits to the study subjects, such as early screening for birth defects. This benefit may facilitate the recruitment of pregnant women into the study. Repeated measurements of growth in infancy and childhood will likely be part of the NCS. The timing of these measurements will require compromises with other aims of the NCS. More comprehensive growth measurements, such as changes in body composition, use well standardized methods in older children and adolescents, are now part of the NHANES, and carry only minimal risks, such as small exposure to radiation for DEXA measurements. Many of these measures will also be critical to investigate other hypotheses, such as those related to the development of peak bone mass. Assessment of obesity co-morbidities, such as blood pressure, fasting glucose, insulin, and lipid profiles are routine medical practice in older children and should not be an overwhelming burden to the subjects or to the study protocol and budget. Blood studies, especially fasting, in younger children, will take more attention. Additionally, these outcomes will likely be of interest for other hypotheses.

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